UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/044,650	01/11/2002	Beth A. Goins	UTSK:343US/TMB	9390

7590 06/29/2005

Thomas M. Boyce, Esq.
FULBRIGHT & JAWORSKI L.L.P.
Suite 2400
600 Congress Avenue
Austin, TX 78701

EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/044,650	GOINS ET AL.	
	Examiner	Art Unit	
	Dave T. Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,29,30,32-34 and 36-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19, 29-30, 32-34, and 36-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 13 2005 has been entered.

Claims 1, 2, 8, 9, 13, 15-19, 30, 32, 33, 36, 37 have been amended, claims 20-28, 31, 35 have been canceled, and claims 39-40 have been added by the amendment filed March 2005.

Claims 1-19, 29-30, 32-34, and 36-40 are pending for examination.

In view of applicant's latest response and evidence submitted by the Oussoren reference (Advanced Drug Delivery Reviews 50, 143-156, 2001), all pending claims are subjected to a new ground of rejection as set forth below.

During an updated search of prior art, a relevant prior art was found, which is US Pat No. 5,690,907 (Lanza et al). The patent is relevant because the patent teaches the concept of employing a sequential three step administration of a biotin coated ligand, an avidin and a lipid encapsulated particles having a bioactive agent complexed therein (see abstract, and columns 4 and 5). However, Lanza et al does not appear to teach or suggest in any the limitation of the claims, wherein a biotin coated ligand complexed to a liposomal having the diameter of less than 500 nm. Further and given the applicant's latest response, which provides sufficient evidence showing a surprising and

unexpected result limited to the enabling scope of the claims, Lanza is not a prior art under any ground of prior art rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is mainly applied to the claimed embodiments as set forth in claims 39 and 40. The newly added claims broadly embrace the step of massaging at any site of the injection step and/or for at least 5 minutes. The only written support is obtained from the working examples, wherein a combination use of a s.c. injection at the dorsal side of a foot of a rat and the time period of 5 minutes is employed. The as-filed specification does not teach or contemplate that a skilled artisan should massage any injection site for at least 5 minutes in any mammal. Note also that the support of the "5 minute" period is not the same as the claimed limitation drawn to "at least 5 minutes". Thus, this is a new matter rejection and a skilled artisan would not have envisioned at

that applicant, the time the invention was made, has possession of the full breadth of the claimed embodiments as set forth in claims 39 and 40.

Claims 1-19, 29-30, 32-34, and 36-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method for delivery and retention of an active agent in one or more targeted lymph nodes, comprising:

a) injecting subcutanously into a mammal at a site a first composition comprising a biotin complexed to a liposomal having the diameter of less than 500 nm; and

b) injecting subcutanously to said mammal adjacent or at said site a second composition comprising an avidin which binds to said biotin,

wherein an active agent is conjugated to either said liposomal particle or said biotin,

and whereby said avidin encounters and causes aggregation of the liposome-ligand complex at, or just prior to reaching, the one or more targeted lymph nodes; and

A method for detecting one ore more sentinel lymph nodes, comprising:

a) injecting subcutanously into a mammal at a site a first composition comprising a biotin complexed to a liposomal particle having the diameter of less than 500 nm; and

b) injecting subcutanously to said mammal adjacent or at said site a second composition comprising an avidin which binds to said biotin,

wherein an active agent chosen from a radioisotope or dye is conjugated to either said liposomal particle or said biotin,

whereby said avidin encounters and causes aggregation of the liposome-ligand complex at, or just prior to reaching, the one or more sentinel lymph nodes, and whereby said sentinel lymph nodes are detectable.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Note also that should the base claims be amended as indicated above, dependent claims 32 and 36 must be canceled, because of the lack of written support and/or reasonable enablement for such specific species at the time the invention was made, as further elaborated in the below stated rejections.

The main thrust of the invention is the concept of injecting two compositions to a mammal in order to target the delivery of any known bioactive agent to lymph nodes, wherein the first injected composition comprises a colloid particle coated with a ligand, *e.g.,* biotin, and wherein the second injected composition comprises an anti-ligand, *e.g.,* avidin. The state of the art of targeted delivery to lymph nodes by using a generic colloid-base system is not conventional and routine at the time the invention was made, see the references cited in the second full par. on page 6 of the specification, Moghimi, Prog, Biophys. Molec. Biol., Vol. 65, 3, pp. 221-249, 1996 (IDS), Oussoren, Biochimica

et Biophysica Acta 1328, 261,272, 1997. One of the important issues that were raised in the cited references including the as-filed specification is the influence of a colloid particle size, its contents. The as-filed specification clearly teaches such on page 13, and specifically states that "if the colloid-ligand composition is too large, it is retained at the site of injection", and that "if the colloid-ligand composition is too small, it is transported from the site of injection into the circulation and is not retained in the lymph nodes". However, the claims as presently pending embrace the use of an enormous number of colloid particles, regardless of their sizes and structures, in order to achieve the targeted delivery of a bioactive agent to lymph nodes for a sufficient amount of time required for the agent's activity. In fact, Oussoren teaches and provides factual evidence (Figure 3A) demonstrating that only smaller liposomes (less than 400 nm in mean size) were able to enter the lymphatic capillaries, and that even with the liposomes with the 400 nm in mean size, roughly more than 80% of the contents remain at the injected site. Even with the size being satisfied, Applicant's latest response further substantiates the unpredictability of the claimed invention as broadly claimed. For example, the response on page 11 states:

> The data presented in Oussoren (1997) does not appear to be related to the liposomal composition aggregating with a second composition-much-less such aggregation occurring "at or just prior to reaching" a targeted site. Additionally, the date in Oussoren (1997) appears to indicate minimal liposome retention in the lymph node. This is confirmed by the same collaborators in Figures 2(b) of

Oussoren and Storm, Advanced Drug Delivery Reviews: 50;143-156 (2001) ("Oussoren (2001)), a copy of which is attached as Appendix A for the convenience of the examiner. By contrast, Applicants' specification provides surprising and unexpected data that shows at least an 11-14 fold increase in liposomal retention in the lymph nodes.

This, it appears that the size of a colloidal particle is not a sole factor in causing the limitation "aggregation at or just prior to at, or just prior to reaching, the one ore more targeted lymph nodes."

The entire as-filed application including its working examples focus mainly on liposomal particles with a <500 nm in diameter and a combination use of a biotin/avidin binding pair.

The state of the prior art, as evidenced by numerous cited references, does show that a delivery and retention of an active agent in one or more targeted lymph nodes so as to effect a diagnostic or therapeutic effect is not routine. It appears that liposomes have been extensively studied and proposed as carriers for the delivery of therapeutic and diagnostic agents to the lymphatic system (see Oussoren 2001, cited by applicants, abstract). In fact, the abstract states:

> Decisive factors influencing lymphatic absorption and lymph node uptake of s.c. administered liposomes are liposome size and the anatomical site of injection.

Further, Oussoren (2001) teaches on page 148, column 2:

The incomplete lymphatic absorption of s.c. administered particles as described above may be the result of interactions between the particle surface and components of the interstitium inducing formation of larger particles that are not taken up by the lymphatic capillaries but will remain at the site of injection.

Neither the prior art of record nor the as-filed application provides any additional working examples showing a combination s.c. administration of a binding affinity pair other than a biotin coated liposome in combination with avidin so as to effect a sufficient "aggregation at or just prior to at, or just prior to reaching, the one ore more targeted lymph nodes."

With respect to the breadth of presently pending claims, which encompasses numerous ligands and anti-ligands other than biotin and avidin, and colloid based systems other than liposomes, Philips WT, (abstract, July 16, 1999, 9th Annual Smposium on Cancer Research in San Antonio, IDS) teaches:

The avidin injection causes aggregation of the biotin coated liposomes that are in the process of migrating through lymphatic vessels. When this aggregated liposome complex reaches the next encountered lymph node, it becomes retained for a prolonged time in this node. This prolonged retention contrasts greatly with control liposome preparations which simply pass through the lymph node without retention.

The specification on pages 23 and 24 acknowledges the same as indicated above by Philips WT.

While the skill level of a person of skilled in the art is relatively high, the breadth of the claimed invention is broad so as to cover a genus of colloidal particles/anti-ligand/ligand regardless of administration routes, sizes with the < 500 nm, surface modification(s), and types of affinity binding pairs. Thus, given the fact that detailed information on factors influencing lymphatic targeted drug delivery remains unsettled within the those of skill in the art, that the as-filed specification does not provide sufficient reasoning and/evidence so as to reasonably correlate between the results of the working examples and the breadth of the claimed invention, and given the reasons set forth, one skilled in the art would not have been able to reasonably extrapolates, from the teachings and/or working examples provided by the specification to the entire breadth of the claimed invention.

Another issue which is essential for the usage within the context of the specification is the teaching provided by the specification on page 15, which clearly teaches that in order for the targeted delivery to the lymph nodes to work, the two compositions must be injected s.c. within a sufficient amount of time and/or at locations, so that the injected anti-ligand would encounter the colloid-ligand at, or just prior to reaching, the targeted lymph node, whereby such encounter would cause aggregation of the colloid-ligand and its subsequent retention at the targeted lymph nodes. See Oussoren (2001, page 150 bridging page 151). As such, the claims are only reasonably enabling for claimed embodiments, wherein such steps are employed in order to have the injected anti-ligand encountering the colloid-ligand at, or just prior to reaching, the targeted lymph node.

With respect to the limitation of "a size range of 5 to 500 nm", and it appears that applicant's claims broadly embrace liposomal particles having a size of 5 nm, it is not apparent how a skilled artisan make such particles at the time the invention was made because neither the prior art nor the specification provides any specific written teaching and/or support/guidance so as to enable a person skilled in the art makes such particles without any undue experimentation at the time the invention was made. Note also that as taught in Oussoren, if the size become too small such as 5 mn, the particles will pass through the lymphatic system without being retained at a lymph node, and thus, given that a retention of a liposomal particle at a lymph node is muti-factor-dependent including the size and a site of injection, there is no evidence and/or guidance for a skilled artisan to reasonably believe that such particles can be reasonable made and use, without any undue experimentation and within the context of the claimed invention, at the time the invention was made.

Thus, it is apparent to one skill in the art, particularly on the basis of the teaching provided by the specification and the state of the art as set forth above, that the application of a liposomal article through a s.c. site, its retention and aggregation property caused by the injected avidin at the site of administration of a biotin coated liposome, are all essential for the targeted delivery and retention a colloidal delivery system as claimed. Thus, the presently pending claims are only reasonably enabling for such claimed embodiments, as set forth above.

In view of reasons set forth above, it would require an undue experimentation for one skilled in the art to practice the full breadth of the claimed invention at the time the invention was made.

Applicant's response (page 6) has been considered by the examiner but is moot in view of the new ground of rejection as set forth above.

All previously cited prior art rejections are withdrawn by the examiner because of the citation of Oussoren (2001, page 150, column 1 bridging column 2) and applicant's response, particularly the response as set forth on pages 9, 11, 13, and 14. The response appears to show that the results obtained from the working example is indeed surprising and unexpected to one of ordinary skill in the art at the time the invention was made.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Ram Shukla*, may be reached at **571-272-0735.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Central Fax number, which is **571-273-8300**.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service

center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER